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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/675,406	09/30/2003	Deepa Eveleigh	5138	7796

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EXAMINER	
JOYCE, CATHERINE	

ART UNIT	PAPER NUMBER
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/675,406	EVELEIGH ET AL.	
	Examiner	Art Unit	
	Catherine M. Joyce	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 February 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2 and 4-15* is/are pending in the application.

4a) Of the above claim(s) *6-15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4 and 5* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

1. The Amendment filed February 12, 2007 in response to the Office Action of October 11, 2006 is acknowledged and has been entered. Claim 3 is canceled, claims 1-2 and 4-15 are pending, claims 6-15 are withdrawn from consideration as being drawn to a non-elected invention, and claims 1-2 and 4-5 are currently being examined.

2. The following rejections are being maintained:

Claim Rejections - 35 USC 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claim 4 remains rejected under 35 USC 112, first paragraph, and claims 1-2 and 5 are newly rejected under 35 USC 112, first paragraph, for the reasons set forth previously in the Paper mailed October 11, 2006, Section 4, pages 2-5.

Applicant argues the following:

(i) that with respect to the Wands factors, the Office Action focused exclusively on the predictability or unpredictability of the art and that none of the other factors are considered;

(ii) that the conclusion in the Office Action that the present invention "would [not] function as claimed" due to a lack of predictability in extrapolating the "cell culture data" of the application to the claimed in vivo method is directly contrary to the Federal Circuit case law, wherein applicant cites In re Brana, 51 F.3d 1560 (Fed. Cir. 1995) as holding that proof of an alleged pharmaceutical property for a compound by statistically significant animal tests is sufficient to reasonably predict the success of the compound in humans;

(iii) that the Office Action characterizes the data of the present specification to be limited to in vitro cell culture data whereas Example 1 describes a mouse tumor

xenograft model wherein the human cancers are originally derived from tissue culture but the experiment involves testing a Raf kinase inhibitor in a xenograft model in an vivo environment and that the mouse model data "correlates" with the claimed invention because the data demonstrate that the level of expression of a biomarker (adrenomedullin) is a useful marker to show the effectiveness of an anticancer treatment;

(iv) (citing In re Wands) that enablement is not precluded by the necessity for some experimentation such as routine screening provided that experimentation needed to practice the invention is not undue experimentation, and that a considerable amount of experimentation is permissible if it is merely routine or if the specification provides a reasonable amount of guidance with respect to the direction of experimentation.

Applicant's arguments have been considered but have not been found to be persuasive. Applicant's first argument that, with regard to the Wand's factors, the Office Action focused exclusively on the predictability or unpredictability of the art and that none of the other factors are considered is not found to be persuasive because the Office Action specifically considered the working examples in the specification, the amount of guidance provided in the specification, and the amount of experimentation required. Applicant's second argument that the conclusion in the Office Action that the present invention "would [not] function as claimed" due to a lack of predictability in extrapolating the "cell culture data" of the application to the claimed in vivo method is directly contrary to the Federal Circuit case law, wherein applicant cites In re Brana, is not found to be persuasive because the facts from the instant case can be distinguished from Brana in that the model employed in the instant specification cannot be reasonably correlated with the claimed invention. Applicant's third argument that Example 1 describes a mouse tumor xenograft model wherein the human cancers are originally derived from tissue culture but the experiment involves testing Raf kinase in a xenograft model in an vivo environment and that the mouse model data "correlates" with the claimed invention are not found to be persuasive in that the exemplified mouse model is not reasonably correlated with the claimed invention because the example does not

teach that the employed kinase inhibitor was effective in the treatment of cancer. Thus a correlation could not be established between the expression of the adrenomedullin biomarker and the effectiveness of the anti-cancer agent, i.e. the Raf kinase inhibitor as claimed. Further, as set forth in the previous Office Action, effects observed with cells derived from cell culture are not predictive of effects observed with cells in vivo and thus the results observed with cells derived from cell culture are not predictive of results observed with cells in vivo. Applicant's fourth argument that enablement is not precluded by the necessity for some experimentation such as routine screening if the specification provides a reasonable amount of guidance with respect to the direction of experimentation is not found to be persuasive because, in the instant case, the specification does not provide sufficient guidance to indicate that the invention would predictably function as claimed even with experimentation.

New Grounds of Rejection

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-2 and 4-5 are rejected under 35 USC 112, first paragraph, as lacking an adequate written description in the specification.

The claims are drawn to a method to monitor the response of a patient being treated for cancer by administering a Raf kinase inhibitor, comprising the steps of: (a) determining the level of expression of one or more one biomarker(s) in a first biological sample taken from the patient prior to treatment with the Raf kinase inhibitor; (b) determining the level of expression of the biomarker in at least a second biological sample taken from the patient subsequent to the initial treatment with the Raf kinase inhibitor; and (c) comparing the level of expression of the biomarker in the second biological sample with the level of expression of the biomarker in the first biological

sample; wherein a change in the level of expression of the biomarker in the second biological sample compared to the level of expression of biomarker in the first biological sample indicates that the effectiveness of the treatment with the Raf kinase inhibitor.

Although drawn to the DNA arts, the finding in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and Enzo Biochem, Inc. V. Gen-Probe Inc. are relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that "[a] written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." Id. At 1567, 43 USPQ2d at 1405. The court also stated that

> a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA" without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is.

Id. At 1568, 43 USPQ2d at 1406. The court concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." Id.

Finally, the court addressed the manner by which a genus of cDNAs might be described. "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." Id.

The Federal Circuit has recently clarified that a DNA molecule can be adequately described without disclosing its complete structure. See Enzo Biochem, Inc. V. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The Enzo court adopted the standard that "the written description requirement can be met by 'show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ....i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics." Id. at 1324, 63 USPQ2d at 1613 (emphasis omitted, bracketed material in original).

Although the inventions at issue in Lilly and Enzo were DNA constructs per se, the holdings of those cases are also applicable to claims such as those at issue here. A disclosure that does not adequately describe a product itself logically cannot adequately describe a method of using that product.

Thus, the instant specification may provide an adequate written description of "a Raf kinase inhibitor" per Lilly by structurally describing a representative number of species of "a Raf kinase inhibitor" or by describing "structural features common to the members of the genus, which features constitute a substantial portion of the genus." Alternatively, per Enzo, the specification can show that the claimed invention is complete "by disclosure of sufficiently detailed, relevant identifying characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics."

In this case, the specification does not describe "a Raf kinase inhibitor" in the claimed method in a manner that satisfies either the Lilly or Enzo standards. The specification does not provide the complete structure of any Raf kinase inhibitors, nor does the specification provide any partial structure of such Raf kinase inhibitors, nor any physical or chemical characteristics of Raf kinase inhibitors, nor any functional characteristics coupled with a known or disclosed correlation between structure and function, other than the description of the Raf kinase inhibitor, ISIS 5132, a

phosphorothioate antisense oligonucleotide. Although the specification discloses a single "Raf kinase inhibitor", this does not provide a description of "a Raf kinase inhibitor" of the claimed methods that would satisfy the standard set out in Enzo.

The specification also fails to describe the claimed "a Raf kinase inhibitor" by the test set out in Lilly. The specification describes only the Raf kinase inhibitor ISIS 5132, a phosphorothioate antisense oligonucleotide. Therefore, it necessarily fails to describe a "representative number" of such species. In addition, the specification also does not describe "structural features common to the members of the genus, which features constitute a substantial portion of the genus."

Thus, the specification does not provide an adequate written description of "a Raf kinase inhibitor" and therefore, does not provide an adequate written description of the claimed method that employs "a Raf kinase inhibitor".

Applicants arguments in response to the rejection set forth in Section 5, pages 5-8 in the Paper mailed October 11, 2006, may be relevant to the instant rejection and are considered here. Applicant argues that the fact that the present application does not describe particular Raf kinase inhibitors or their structures does not violate existing law of the Federal Circuit pertaining to written description. Applicant further argues that the court recently indicated in Falkner v. Inglis, 448 F.3d 1357 (Fed. Cir. 2006) that "(1) examples are not necessary to support the adequacy of a written description; (2) the written description standard may be met even where actual reduction to practice of an invention is absent; and (3) there is no per se rule that an adequate written description of an invention that involves a biological macromolecule must contain a recitation of known structure" (citing Falkner at 1366). Applicants further argue that the court especially noted that "it is the binding precedent of this court that Eli Lilly does not set forth a per se rule that whenever a claim limitation is directed to a macromolecular sequence, the specification must always recite the gene or sequence, regardless of whether it is known in the prior art" (citing Falkner at 1367) and that "where...accessible literature sources clearly provided, as of the relevant date, genes and their nucleotide sequences (here "essential genes"), satisfaction of the written description requirement

does not require either the recitation or incorporation by reference (where permitted) of such genes and sequences" citing Falkner at 1358). Applicant further argues that numerous Raf kinase inhibitors are known and described in the art (citing Raf kinase inhibitors described in U.S. Patent No. 7,071,216, which also incorporates by reference the Raf kinase inhibitors described in (a) Crump, Current Pharmaceutical Design, 2002, 8:2243-2248, (b) Sebastien et al., Current Pharmaceutical Design, 2002, 8:2249-2253, (c) Kolch et al., Nature, 1991, 349:416-428, (d) Monia et al., Nature Medicine, 1996, 2:668-675, and (e) U.S. Patent Nos. 6,458,813, 6,391,636, 6,358,932, 6,268,391, 6,204,467, 6,037,136 and 5,717,100). Applicant further argues that, under Falkner, Applicants should not be required to have disclosed particular Raf kinases or their structures in order to fulfill the requirements of written description.

Applicant's arguments have been considered but have not been found to be persuasive because, while the art may provide structure for various Raf kinase inhibitors, the instant specification has not established a correlation between structure and function for any Raf kinase inhibitor and thus a class of Raf kinase inhibitors that would function as claimed in the specification has not been described. For example, Raf kinase inhibitors may function by inhibiting different aspects of Raf kinase activity and without the desription of at least Raf kinase inhibitor that would function as claimed one of skill in the art could not determine that the inventors were in possession of the claimed invention at the time the application was filed.

7. All other objections and rejections recited in the previous Office Action are hereby withdrawn.

8. No claims allowed.

9. Applicant's amendment necessitated the new grounds of rejection. Accordingly, **THIS ACTION IS MADE FINAL**. See M.P.E.P. § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE

MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Catherine M. Joyce whose telephone number is 571-272-3321. The examiner can normally be reached on Monday thru Friday, 10:15 - 6:45.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley, can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8700.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Catherine M. Joyce
Examiner
Art Unit 1642

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